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3,754,021

4-KETO-4-(3'-CHLORO-4'-CYCLOHEXYL)PHENYL-BUTYRIC ACID AND RELATED COMPOUNDS

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5 Claims

ABSTRACT OF THE DISCLOSURE

The preparation of various cyclohexylphenyl keto and hydroxy butyric acids and derivatives, the processes for preparing them, and their method of treatment as anti-inflammatory agents, are disclosed.

BACKGROUND OF THE INVENTION

There have been a great many new anti-inflammatory drugs in the past two decades. Most of these have been steroids of the 11-oxygenated pregnane series. These, while highly effective, have a drawback of causing many side effects. There is a need for equally effective compounds of much simpler structure and having less side effects. It has been found that 4-aryl-3-hydroxy butyric acids have anti-inflammatory properties (South African Patent No. 65/3510).

It is known that succinic anhydrides react with alkyl benzene compounds to form alkylbenzoyl propionic acids by a Friedel-Crafts reaction. Methods for preparing benzoyl propionic acids are shown in the September issue reviews of Friedel-Crafts reactions of Industrial and Engineering Chemistry, K. Le Roi Nelson, volume 47, No. 9, page 1926 (1955); volume 48, No. 9, page 1670 (1956); volume 49, No. 9, page 1560 (1957); and volume 50, No. 9, page 1414 (1958).

SUMMARY OF THE INVENTION

New cyclohexylphenyl keto butyric and cyclohexylphenylhydroxy butyric acids and derivatives, the processes for making them, and a method of treatment using them as medicinal agents, are the subject of this invention. The disclosed class of compounds in this invention exhibit anti-inflammatory activity and are effective in the prevention and inhibition of edema and granuloma tissue formation.

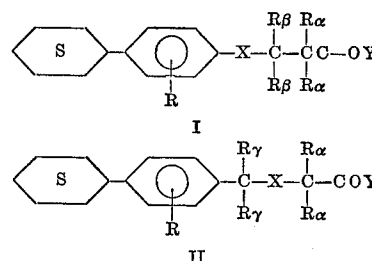
DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention discloses new compounds which are valuable medicinal agents because of their effectiveness in preventing and inhibiting edema and granuloma tissue formation. This invention describes new compounds which contain a keto or hydroxy group attached at the β or γ positions of a γ -substituted aryl butyric acid. It further describes related derivatives of these γ -substituted aryl butyric acids, namely, the non-toxic pharmaceutically acceptable salts, esters and amides. This invention also describes the method of preparation to the instant β - and γ -keto and β - and γ -hydroxy substituted butyric acids and derivatives. Still further, it describes the method of treating inflammation by the administration of these compounds.

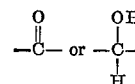
More specifically, this invention describes β - and γ -keto and hydroxy butyric acids which are attached at the γ -position to a p-cyclohexylphenyl group in which both the butyric acid chain and the phenyl ring may be substituted.

In a more narrow aspect, the present invention embraces that series of compounds having the following structural formulas:

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where
X is



R_α , R_β and R_γ are hydrogen, alkyl (preferably lower alkyl such as methyl, ethyl, propyl, etc.), cycloalkyl (preferably cyclolower alkyl such as cyclopropyl, cyclobutyl, etc.), aryl (preferably mononuclear aryl such as phenyl, tolyl, xylyl, etc.), aralkyl (preferably mononuclear ar-lower alkyl such as benzyl, phenethyl, etc.);

R_α together with R_β , R_β together with R_γ , and R_γ together with R_α are alkenyl (preferably lower alkenyl such as methylene, ethylene, etc.), or cycloalkyl (preferably cyclolower alkyl such as cyclopropyl, cyclobutyl, etc.);

R_α together with R_β is a double or triple bond, part of a cycloalkyl ring (preferably part of a cyclolower alkyl ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), part of a cycloalkenyl ring (preferably part of a cyclolower alkenyl ring such as cyclopentenyl, cyclohexenyl, etc.), or part of an aryl ring (preferably part of a mononuclear aryl ring such as phenyl, tolyl, etc.);

R is hydrogen, nitro, amino, mono- and di-alkyl amino (preferably mono- and di-lower alkyl amino such as methylamino, ethylamino, dimethylamino, ethylmethylamino, etc.), halo (preferably chloro, bromo, fluoro, etc.), alkoxy (preferably lower alkoxy such as methoxy, ethoxy, propoxy, etc.) or hydroxy;

Y is —OH, —NH₂, alkylamino (preferably lower alkylamino such as methylamino, ethylamino, etc.), dialkylamino (preferably di(lower alkyl)amino such as dimethylamino, methylethylamino, etc.), cycloalkylamino (preferably cyclolower alkylamino such as cyclopropylamino, cyclobutylamino, etc.), N-teterocyclo (preferably N-piperidino, N-morpholino, N-piperazino, N-homopiperazino, N-pyrrolidino, etc.), alkoxy (preferably lower alkoxy such as methoxy, ethoxy, etc.), benzyloxy and OM, where M in general is any base which will form an acid addition salt with a carboxylic acid and whose pharmacological properties will not cause an adverse physiological effect when ingested by the body system (preferably an alkali, alkaline earth or aluminum metal such as sodium, potassium, calcium, magnesium and aluminum metals).

In structure I, when X is



and Y is —OH, then R_α , R_β and R cannot all be hydrogen at the same time.

In structure II, when X is

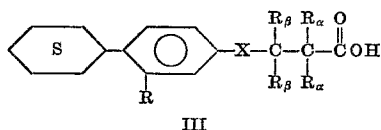
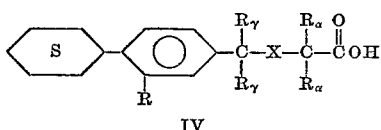


and Y is —OH, lower alkoxy or amino, then R_α and R_γ cannot all be hydrogen at the same time when R is hydrogen, halo or alkoxy.

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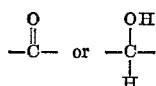
R may be substituted at any position of the phenyl ring (preferably in the 3'-position).

The more preferred compounds of this invention relate to those compounds of structures I and II, having the following formulas:



where

X is



R_α, R_β and R_γ are hydrogen, alkyl (preferably lower alkyl such as methyl, ethyl, propyl, etc.);

R_α together with R_β forms a double bond; R is hydrogen, nitro, amino, hydroxy or chloro.

Representative compounds of this invention are as follows:

4-keto-4-(3'-nitro-4'-cyclohexyl)phenyl butyric acid
 3-keto-4-(3'-nitro-4'-cyclohexyl)phenyl butyric acid
 4-hydroxy-4-(3'-nitro-4'-cyclohexyl)phenyl butyric acid
 3-hydroxy-4-(3'-nitro-4'-cyclohexyl)phenyl butyric acid
 4-keto-4-(3'-chloro-4'-cyclohexyl)phenyl butyric acid
 3-keto-4-(3'-chloro-4'-cyclohexyl)phenyl butyric acid
 4-hydroxy-4-(3'-chloro-4'-cyclohexyl)phenyl butyric acid
 3-hydroxy-4-(3'-chloro-4'-cyclohexyl)phenyl butyric acid
 4-keto-4-p-cyclohexylphenyl-2-methyl butyric acid
 3-keto-4-p-cyclohexylphenyl-2-methyl butyric acid
 4-keto-4-p-cyclohexylphenyl-2,2-dimethyl butyric acid
 4-keto-4-p-cyclohexylphenyl-3-methyl butyric acid
 4-keto-4-p-cyclohexylphenyl-3,3-dimethyl butyric acid
 4-keto-4-p-cyclohexylphenyl-2,3-dimethyl butyric acid
 4-keto-4-(3'-amino-4'-cyclohexyl)phenyl butyric acid
 4-keto-4-(3'-hydroxy-4'-cyclohexyl)phenyl butyric acid
 4-keto-4-(3'-nitro-4'-cyclohexyl)phenyl-2-butenic acid

This invention further relates to a method of treating inflammation by the administration of compounds having the general Formulas I and II.

Another aspect of this invention relates to the method for the relief of inflammation in a patient which comprises the administration of compounds having the structural Formulas III and IV. This foregoing class of acids shows particularly good anti-inflammatory activity and represents a preferred subgroup of compounds within the scope of this invention.

We have found that the compounds of this invention have a useful degree of anti-inflammatory activity and are effective in the treatment of arthritic and dermatological disorders and in like conditions which are responsive to treatment with anti-inflammatory agents. For these purposes, they are normally administered orally in tablets or capsules, the optimum dosage depending, of course, on the particular compound being used and the type and severity of the condition being treated. Although the optimum quantities of the compounds of this invention to be used in such manner would depend on the compound employed and the particular type of disease condition treated, oral dose levels of preferred compounds in the range of 0.5 to 30 mg. per kilogram (preferably in the range of 3 to 15 mg. per kilogram per day) are useful in control of arthritic conditions, depending on the activ-

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ity of the specific compound and the reaction sensitivity of the patient.

Various tests in animals have been carried out to show the ability of compounds of this invention to exhibit reactions that can be correlated with anti-inflammatory activity in humans. One such test used is the carrageenin testing method, which is known to correlate well with anti-inflammatory activity in humans and which is a standard test used to determine anti-inflammatory activity. This test shows the ability of compounds to inhibit edema induced by injection of an inflammatory agent into the tissue of the foot of a rat against non-treated controls. This is outlined in detail by C. A. Winter, Proceedings Society of Experimental Biology and Medicine, 1962, III, 544. This correlation has been shown by the activities of compounds known to be clinically active, including Indocin, Aspirin, Butazolidine, Tandearil, Cortone, Hydrocortone and Decadron. In view of the results of this test, the instant compounds can be considered to be active anti-inflammatory agents.

In addition to the pharmacological activity, the β- and γ-keto and hydroxy p-cyclohexylphenyl butyric acid products of this invention are useful as intermediates in preparing the ester and amide derivatives described and claimed herein. The said ester and amide derivatives also exhibit anti-inflammatory activity and therefore are useful in the treatment of these disorders.

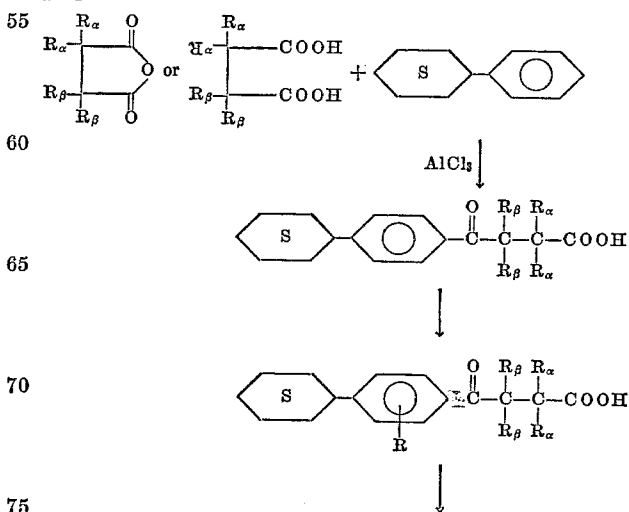
The β- and γ-keto and hydroxy p-cyclohexylphenyl butyric acids and derivatives of this invention are conveniently prepared by the following reactions:

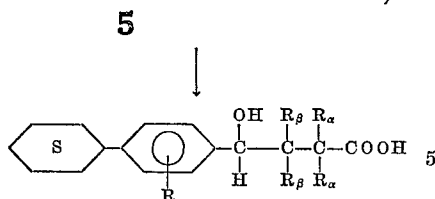
Method I

(a) Succinic anhydrides and carboxylic acids react with cyclohexylbenzene under the conditions of the Friedel-Crafts reaction with the formation of γ-keto butyric acids. It is preferred that the reaction be carried out in an inert solvent and that for each mole of anhydride two moles of aluminum chloride should be used. The product of this reaction can then be nitrated and the nitrated product used for further structure modification.

(b) The γ-keto butyric acids can be conveniently reduced to the corresponding γ-hydroxy butyric acids. Hydrogenation using heterogeneous catalysts may be employed in preparing the desired alcohols. Such heterogeneous catalysts used may be solid phase metal catalysts (such as platinum, palladium, rhodium, ruthenium, etc.), active catalysts containing a metal catalyst on a suitable charcoal carrier (such as 5 to 10% palladium-on-carbon, etc.) or Raney nickel. Any conventional reaction conditions for carrying out the hydrogenation of a ketone to an alcohol may be employed.

The following equation illustrates this method of preparation:





where R_α , R_β and R are as described above.

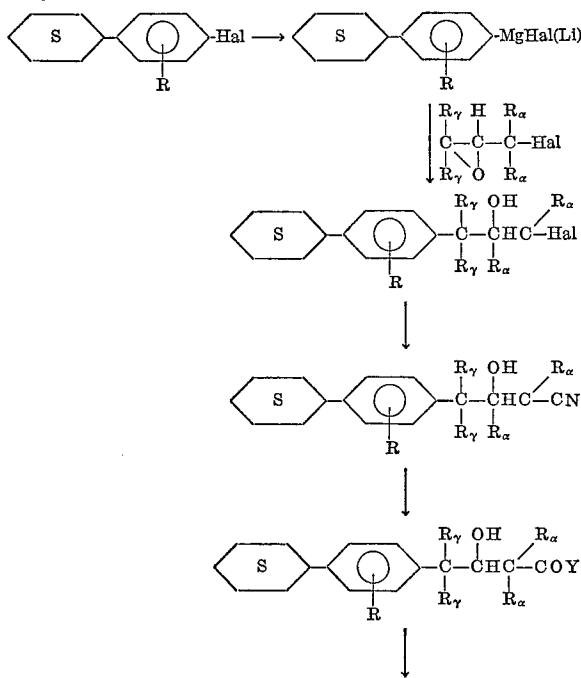
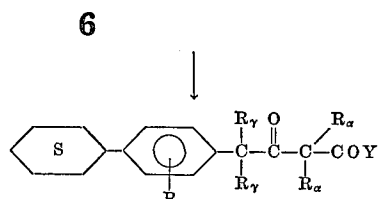
Method II

(a) When a p-cyclohexylphenylhalo compound is treated with magnesium or lithium, an organo-metallic compound is formed. This organo-metallic Grignard or lithium derivative is then treated with a substituted 2,3-epoxypropyl halide (preferably a 2,3-epoxypropyl chloride) and the corresponding 3-p-cyclohexylphenyl-2-hydroxypropyl halide is formed.

(b) The corresponding nitrile is then formed by treatment with an alkali metal cyanide (preferably potassium cyanide) in a solvent (preferably in a dimethyl sulfoxide aqueous or anhydrous alcohol solvent). The nitrile may be heated in solution with an appropriate alcohol containing one mole equivalent of water in the presence of an acidic catalyst (preferably hydrogen chloride) to form the corresponding ester. The ester may then be converted into the corresponding acid while warming with aqueous alkaline hydroxide solution. The nitrile may also be converted directly into the corresponding acid by heating with a concentrated mineral acid (preferably hydrochloric acid) in the presence of a lower alkanol to assist solution of the nitrile. The nitrile may further be converted into the amide by warming with hydrogen peroxide in the presence of an alkali. The amide may then be hydrolyzed to the acid by heating with a solution of an alkali hydroxide (preferably sodium or potassium hydroxide).

(c) Oxidation of the β -alcohols to β -ketones can be conveniently carried out in an aqueous medium, keeping the temperature between 10° C. to 100° C. (preferably 20° C. to 40° C.). The oxidation can be carried out in a suitable oxidizing medium which is normally employed for the preparation of ketones from the alcohols. One such mixture is a sulfuric-chromic acid mixture. This oxidation further can be carried out on the acid ester or amide derivatives.

The following reaction equations illustrate this method of preparation:



where R_α , R_β , R and Y are as described above.

Method III

The ester and amide derivatives of the instant carboxylic acid products can also be prepared by conventional methods well known to those skilled in the art. Thus, for example, the ester derivatives may be prepared by the reaction of a β - or γ -keto or hydroxy p-cyclohexylphenyl butyric acid with an alcohol such as with a lower alkanol in the presence of a suitable catalyst such as in the presence of sulfuric acid, boron trifluoride etherate, dry hydrogen chloride gas and the like, or, alternatively, the starting acid may be converted to its acid halide by conventional methods and the acid halide thus formed may be reacted with an appropriate lower alkanol, providing the R group present will not react (such as the $-\text{OH}$ group). The methyl ester of the saturated compounds may also be prepared in the usual manner with diazomethane.

The amide derivatives of the instant β - and γ -keto and hydroxy p-cyclohexylphenyl butyric acids may be prepared by treating the acid halide of the said products with ammonia or with an appropriate monoalkylamine, dialkylamine, cycloalkylamine or heterocyclic amine (such as pyrrolidine, piperidine, piperazine, homopiperazine, morpholine, and the like) to produce the corresponding amide, provided the R group present will not react (such as $-\text{OH}$). Still another process for preparing the said amide derivatives comprises converting an ester derivative of the instant acid compounds to its corresponding amide by treating said ester with ammonia or with an appropriate monoalkylamine, dialkylamine or heterocyclic amine to produce the corresponding amide derivative. These and other equivalent methods for the preparation of the ester and amide derivatives of the instant products will be apparent to those having ordinary skill in the art.

This invention further relates to the acid addition salts formed by the action of a suitable base with a carboxylic acid. Suitable bases thus include, for example, the alkali metal alkoxides such as sodium methoxide, etc., and the alkali metal and alkaline earth metal hydroxides, carbonates, bicarbonates, etc. (such as sodium hydroxide, potassium hydroxide, calcium hydroxide, potassium carbonate, sodium bicarbonate, magnesium bicarbonate, etc.). Also the aluminum salts of the instant products may be obtained by treating the corresponding sodium salt with an appropriate aluminum complex such as aluminum chloride hexahydrate, etc. The acid addition salts thus obtained are the functional equivalent of the corresponding β - and γ -keto and hydroxy p-cyclohexylphenyl butyric acid products and one skilled in the art will appreciate that to the extent that the instant carboxylic acids are useful in therapy, the variety of acid addition salts embraced by this invention are limited only by the criterion that the bases employed in forming the salts be both non-toxic and physiologically acceptable.

Appropriately desired end-products having various R substituents can be prepared using suitable reactions in order to convert one R group to another. Thus, for example, using conventional methods, the β - and γ -keto and hydroxy p-cyclohexylphenyl butyric acids and derivatives can be nitrated and the resulting nitro compounds subsequently converted to the desired R substituent. It is to be understood, however, that the conversion of the nitro group may also be accomplished at various stages along the way toward producing the final product. For example, when a 3'-substituted compound is desired, ni-

tration of the unsubstituted β - or γ -hydroxy or keto p-cyclohexylphenyl butyric acid or derivatives results in the 3'-nitro products. This nitro group can then be converted to the corresponding 3'-R substituents by appropriate reactions; for example, the nitro compound can be reduced in the presence of palladium under an atmosphere of hydrogen to form the 3'-amino compound. This amino compound may then be reacted with an organic halide such as methyl halide to form the mono- or di-substituted amino compound. The amino compound may also be diazotized and the diazo group replaced by a hydroxyl group which, in turn, may be alkylated to form a 3'-lower alkoxy group. The diazonium salt derived from the amino compound may also be treated with ethyl xanthate, followed by saponification of the xanthate under alkaline conditions to give the mercapto compound. Also, the diazonium compound may be reacted with a cuprous halide in a cold medium under acid conditions to form the 3'-halide compound or reacted with cuprous cyanide to form a 3'-cyano compound.

The products of this invention can contain asymmetric carbon atoms and therefore may be obtained as racemic mixtures or as dextro and levorotatory isomers. These may be separated by any of the various methods of resolution. A method that may be employed is combining the racemic compound with an optionally active compound, for example, by salt formation. Two products are then obtained. If the instant acids are added to an optically active base, such as the dextro-rotatory alkaloid cinchonine, then the salts produced possess different properties and different solubilities and can be separated by fractional crystallization. When the salts have been completely separated by repeated crystallizations, the base is split off and the pure d- or l-acids are obtained.

The starting materials employed in the foregoing methods have previously been prepared. p-Cyclohexylbenzene, p-cyclohexylphenyl halides and succinic anhydrides and acids have been described in the literature and many are commercially available.

The following are a group of detailed examples which show the preparation of desired compounds of this invention. They are to be construed as illustrations of the invention and not as limitations thereof.

EXAMPLE 1

4-keto-4-p-cyclohexylphenyl butyric acid

In 150 ml. of dry ethylene chloride is dissolved 26 g. of aluminum chloride, 16.5 g. of phenylcyclohexane and 12.8 g. of succinic anhydride. This is stirred for two days and then poured onto 200 ml. of cold 1:1 hydrochloric acid-water. The mixture is then extracted with chloroform, dried over sodium sulfate and concentrated in vacuo to yield 4-keto-4-p-cyclohexylphenyl butyric acid as a solid, which is washed with hot hexane and recrystallized from benzene (M.P. 131-136° C.).

Following the procedure of Example 1 above, but substituting for succinic anhydride an equimolar amount of the starting materials in Table I below, there is obtained the corresponding product of Table II below.

TABLE I

methyl succinic anhydride
ethyl succinic acid
 α,α -dimethyl succinic anhydride
 α,β -dimethyl succinic anhydride
tetramethyl succinic acid
cyclohexyl succinic anhydride
phenyl succinic anhydride
 α,β -diphenyl succinic anhydride
benzyl succinic anhydride
itaconic anhydride
teraconic anhydride
maleic anhydride
citraconic anhydride

α,β -dimethyl maleic anhydride
phenyl maleic anhydride
2-butyndioic acid
5 1-cyclohexene-1,2-dicarboxylic acid anhydride
1-cyclopentene-1,2-dicarboxylic acid anhydride
3-cyclohexene-1,2-dicarboxylic acid anhydride
cyclopropane-1,2-dicarboxylic acid
10 cyclohexane-1,2-dicarboxylic acid anhydride
phthalic acid anhydride
4-nitrophthalic acid anhydride
2,3-pyridinedicarboxylic acid anhydride
tetrahomophthalic acid anhydride
tetraphenyl-1,2-phthalic anhydride
15 4,5-imidazoledicarboxylic acid

TABLE II

4-keto-4-(p-cyclohexylphenyl)-2-methylbutyric acid
4-keto-4-(p-cyclohexylphenyl)-2-ethylbutyric acid
20 4-keto-4-(p-cyclohexylphenyl)-2,2-dimethylbutyric acid
4-keto-4-(p-cyclohexylphenyl)-2,3-dimethylbutyric acid
4-keto-4-(p-cyclohexylphenyl)-2,2,3,3-tetramethylbutyric acid
4-keto-4-(p-cyclohexylphenyl)-2-cyclohexylbutyric acid
25 4-keto-4-(p-cyclohexylphenyl)-2-phenylbutyric acid
4-keto-4-(p-cyclohexylphenyl)-2,3-diphenylbutyric acid
4-keto-4-(p-cyclohexylphenyl)-2-benzylbutyric acid
4-keto-4-(p-cyclohexylphenyl)-2-methylenebutyric acid
30 4-keto-4-(p-cyclohexylphenyl)-2-isopropylenebutyric acid
4-keto-4-(p-cyclohexylphenyl)-2-butenic acid
4-keto-4-(p-cyclohexylphenyl)-2-methyl-2-butenic acid
4-keto-4-(p-cyclohexylphenyl)-2,3-dimethyl-2-butenic acid
35 4-keto-4-(p-cyclohexylphenyl)-2-phenyl-2-butenic acid
4-keto-4-(p-cyclohexylphenyl)-2-butyric acid
4-keto-4-(p-cyclohexylphenyl)-[2,3-a]-1-cyclohexenebutyric acid
4-keto-4-(p-cyclohexylphenyl)-[2,3-a]-cyclopentenebutyric acid
40 4-keto-4-(p-cyclohexylphenyl)-[2,3-c]-cyclohexenebutyric acid
4-keto-4-(p-cyclohexylphenyl)-2,3-cyclopropanebutyric acid
4-keto-4-(p-cyclohexylphenyl)-[2,3-a]-cyclohexanebutyric acid
45 4-keto-4-(p-cyclohexylphenyl)-[2,3-a]-benzenebutyric acid
4-keto-4-(p-cyclohexylphenyl)-[2,3-c]-nitrobenzenebutyric acid
50 4-keto-4-(p-cyclohexylphenyl)-[2,2-b]-pyridinebutyric acid
4-keto-4-(p-cyclohexylphenyl)-[2,3-a]-tetrabromobenzenebutyric acid
55 4-keto-4-(p-cyclohexylphenyl)-[2,3-a]-tetraphenylbenzenebutyric acid
4-keto-4-(p-cyclohexylphenyl)-[2,3-d]-imidazolebutyric acid

EXAMPLE 2

3-(p-cyclohexylphenyl)-2-hydroxypropyl chloride

To a stirred solution of .05 mole of p-cyclohexylphenylmagnesium bromide in 250 ml. of anhydrous ether is added 0.05 mole of 2,3-epoxypropyl chloride, keeping the reaction mixture at a gentle reflux. After the addition is complete, the mixture is allowed to stand overnight and then decomposed with 2 N hydrochloric acid. The ether layer is separated, washed with water, dried over sodium sulfate and concentrated in vacuo to yield 3-(p-cyclohexylphenyl)-2-hydroxypropyl chloride as an oil (B.P. 130-132° C./0.1 mm.).

Following the procedure of Example 2 above, but substituting for 2,3-epoxypropyl chloride an equimolar amount of the starting materials in Table I below, there is obtained the corresponding product of Table II following.

TABLE I

2-chloro-3,4-epoxybutane
 2-chloro-2-methyl-3,4-epoxybutane
 2,3-epoxy-1-phenylpropyl chloride
 2,3-epoxy-1-benzylpropyl chloride
 1-epoxyethylcyclohexyl chloride
 2,3-epoxybutyl chloride
 3-phenyl-2,3-epoxypropyl chloride
 3-benzyl-2,3-epoxypropyl chloride
 3-cyclopropyl-2,3-epoxypropyl chloride
 2-chloro-3,4-epoxypentane

TABLE II

2-chloro-4-(p-cyclohexylphenyl)-3-hydroxybutane
 2-chloro-4-(p-cyclohexylphenyl)-3-hydroxy-2-methylbutane
 3-(p-cyclohexylphenyl)-2-hydroxy-1-phenylpropyl chloride
 1-benzyl-3-(p-cyclohexylphenyl)-2-hydroxypropyl chloride
 2-(p-cyclohexylphenyl)-1-(1'-chlorocyclohexyl)ethanol
 3-(p-cyclohexylphenyl)-2-hydroxybutyl chloride
 3-phenyl-3-(p-cyclohexylphenyl)-2-hydroxypropyl chloride
 3-benzyl-3-(p-cyclohexylphenyl)-2-hydroxypropyl chloride
 3-cyclopropyl-3-(p-cyclohexylphenyl)-2-hydroxypropyl chloride
 4-(p-cyclohexylphenyl)-3-hydroxy-2-chloropentane

EXAMPLE 3

4-(p-cyclohexylphenyl)-3-hydroxybutyronitrile

A solution of 0.05 mole of 3-(p-cyclohexylphenyl)-2-hydroxypropyl chloride in 400 ml. ethanol is treated with a solution of 0.06 mole potassium cyanide in 50 ml. H₂O and refluxed for 1½ hours. This is then cooled and poured onto an ice-water mixture, extracted with chloroform, dried over sodium sulfate and concentrated in vacuo to yield 4-(p-cyclohexylphenyl)-3-hydroxybutyronitrile as an oil (B.P. 155° C./0.1 mm.).

Following the procedure of Example 3 above, but substituting each of the compounds from Table II, Example 2, in place of 3-(p-cyclohexylphenyl)-2-hydroxypropyl chloride, there is obtained the corresponding product of Table I below.

TABLE I

4-(p-cyclohexylphenyl)-3-hydroxy-2-cyanobutane
 4-(p-cyclohexylphenyl)-3-hydroxy-2-methyl-2-cyanobutane
 4-(p-cyclohexylphenyl)-3-hydroxy-2-phenylbutyronitrile
 4-(p-cyclohexylphenyl)-3-hydroxy-2-benzylbutyronitrile
 2-(p-cyclohexylphenyl)-1-(1'-cyanocyclohexyl)ethanol
 4-(p-cyclohexylphenyl)-3-hydroxypentanitrile
 4-methyl-4-(p-cyclohexylphenyl)-3-hydroxypentanitrile
 4-phenyl-4-(p-cyclohexylphenyl)-3-hydroxybutyronitrile
 4-benzyl-4-(p-cyclohexylphenyl)-3-hydroxybutyronitrile
 4-cyclopropyl-4-(p-cyclohexylphenyl)-3-hydroxybutyronitrile
 4-(p-cyclohexylphenyl)-3-hydroxy-2-methylpentanonitrile

EXAMPLE 4

Ethyl 4-(p-cyclohexylphenyl)-3-hydroxybutyrate

A solution of 0.4 mole of 4-(p-cyclohexylphenyl)-3-hydroxybutyronitrile in 250 ml. ethanol containing 1 mole equivalent of H₂O, is saturated with hydrogen chloride gas and refluxed for 5 hours. This is then cooled, resaturated with hydrogen chloride gas, and again heated under reflux for 5 hours. The solution is then cooled, poured into water, and extracted with chloroform. The chloroform is then washed with water, dried over sodium sulfate and concentrated in vacuo to yield ethyl 4-(p-cyclohexylphenyl)-3-hydroxybutyrate as an oil (B.P. 150° C./0.1 mm.).

Following the procedure of Example 4 above, but substituting each of the compounds from Table I, Example 3, in place of 4-(p-cyclohexylphenyl)-3-hydroxybutyronitrile, there is obtained the corresponding product of Table I below.

TABLE I

ethyl 4-(p-cyclohexylphenyl)-3-hydroxy-2-methylbutyrate
 ethyl 4-(p-cyclohexylphenyl)-3-hydroxy-2,2-dimethylbutyrate
 ethyl 4-(p-cyclohexylphenyl)-3-hydroxy-2-phenylbutyrate
 ethyl 4-(p-cyclohexylphenyl)-3-hydroxy-2-benzylbutyrate
 1-(1'-carbethoxycyclohexyl)-2-(p-cyclohexylphenyl)ethanol
 ethyl 4-(p-cyclohexylphenyl)-3-hydroxypentanoate
 ethyl 4-(p-cyclohexylphenyl)-4-methyl-3-hydroxypentanoate
 ethyl 4-(p-cyclohexylphenyl)-4-phenyl-3-hydroxybutyrate
 ethyl 4-(p-cyclohexylphenyl)-4-benzyl-3-hydroxybutyrate
 ethyl 4-(p-cyclohexylphenyl)-4-cyclopropyl-3-hydroxybutyrate
 ethyl 4-(p-cyclohexylphenyl)-2-methyl-3-hydroxypentanoate

EXAMPLE 5

4-(p-cyclohexylphenyl)-3-hydroxybutyric acid

A mixture of 0.3 mole ethyl 4-(p-cyclohexylphenyl)-3-hydroxybutyrate in 200 cc. ethanol and a solution of 12 g. (0.3 mole) sodium hydroxide and 25 ml. of water, is heated on a steam-bath for three hours. The reaction mixture is then cooled and poured into 0.5 N hydrochloric acid. The acidic mixture is then extracted with chloroform, dried, and concentrated in vacuo. The resulting 4-(p-cyclohexylphenyl)-3-hydroxybutyric acid is recrystallized from benzene.

Following the procedure of Example 5 above, but substituting each of the compounds from Table I, Example 4, in place of ethyl 4-(p-cyclohexylphenyl)-3-hydroxybutyrate, there is obtained the corresponding product of Table I below.

TABLE I

4-(p-cyclohexylphenyl)-3-hydroxy-2-methylbutyric acid
 4-(p-cyclohexylphenyl)-3-hydroxy-2,2-dimethylbutyric acid
 4-(p-cyclohexylphenyl)-3-hydroxy-2-phenylbutyric acid
 4-(p-cyclohexylphenyl)-3-hydroxy-2-benzylbutyric acid
 1-(1'-carboxycyclohexyl)-2-(p-cyclohexylphenyl)ethanol
 4-(p-cyclohexylphenyl)-3-hydroxypentanoic acid
 4-(p-cyclohexylphenyl)-4-methyl-3-hydroxypentanoic acid
 4-(p-cyclohexylphenyl)-4-phenyl-3-hydroxybutyric acid
 4-(p-cyclohexylphenyl)-4-benzyl-3-hydroxybutyric acid
 4-(p-cyclohexylphenyl)-4-cyclopropyl-3-hydroxybutyric acid
 4-(p-cyclohexylphenyl)-2-methyl-3-hydroxypentanoic acid

EXAMPLE 6

4-(p-cyclohexylphenyl)-3-ketobutyric acid

To a solution of 0.1 mole of 4-(p-cyclohexylphenyl)-3-hydroxybutyric acid in 100 cc. of glacial acetic acid, is added dropwise, with vigorous stirring, a solution of 0.1 mole of chromic acid in 50 cc. of 80% acetic acid. The temperature of the reaction mixture is not allowed to rise above 50° during the addition. The reaction mixture is then stirred at room temperature for 24 hours, poured into 500 cc. of water, and extracted well with benzene. The combined benzene extracts are washed well with water, dried over sodium sulfate, and concentrated to give 4-(p-cyclohexylphenyl)-3-ketobutyric acid.

Following the procedure of Example 6, but substituting for 4-(p-cyclohexylphenyl)-3-hydroxybutyric acid each of the acid products of Table I, Example 5, there is obtained the corresponding 3-ketobutyric acid product of Table I following.

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TABLE I

4-(p-cyclohexylphenyl)-3-keto-2-methylbutyric acid
 4-(p-cyclohexylphenyl)-3-keto-2,2-dimethylbutyric acid
 4-(p-cyclohexylphenyl)-3-keto-2-phenylbutyric acid
 4-(p-cyclohexylphenyl)-3-keto-2-benzylbutyric acid
 4-(p-cyclohexylphenyl)-3-keto-2-cyclohexylbutyric acid
 4-(p-cyclohexylphenyl)-3-ketopentanoic acid
 4-(p-cyclohexylphenyl)-4-methyl-3-ketopentanoic acid
 4-(p-cyclohexylphenyl)-4-phenyl-3-ketobutyric acid
 4-(p-cyclohexylphenyl)-4-benzyl-3-ketobutyric acid
 4-(p-cyclohexylphenyl)-4-cyclopropyl-3-ketobutyric acid
 4-(p-cyclohexylphenyl)-2-methyl-3-ketopentanoic acid

EXAMPLE 7

4-hydroxy-3-(p-cyclohexylphenyl)butyric acid

A solution of 0.045 mole of 4-keto-4-(p-cyclohexylphenyl)butyric acid and 0.05 mole of sodium hydroxide in 100 ml. of water is added slowly to a mixture of 0.02 mole of sodium borohydride in 50 ml. of water. The mixture is heated at 60–75° C. for 1 hour and then refluxed for ½ hour with an additional 0.15 mole of sodium hydroxide. The reaction mixture is then cooled, acidified, and the resulting 4-hydroxy-4-(p-cyclohexylphenyl)butyric acid collected by filtration.

Following the procedure of Example 7, but substituting for 4-keto-4-(p-cyclohexylphenyl)butyric acid each of the acid products of Table II, Example 1, there is obtained the corresponding reduced product of Table I below.

TABLE I

4-hydroxy-4-(p-cyclohexylphenyl)-2-methylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-ethylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2,2-dimethylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2,3-dimethylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2,2,3,3-tetramethylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-cyclohexylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-phenylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2,3-diphenylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-benzylbutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-methylenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-isopropylenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-butenic acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-methyl-2-butenic acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2,3-dimethyl-2-butenic acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-phenyl-2-butenic acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2-butyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-a]-1-cyclohexenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-c]-cyclohexenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-a]-cyclopentenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-2,3-cyclopropanebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-a]-cyclohexenebutyric acid

4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-a]-benzenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-c]-nitrobenzenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-b]-pyridinebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-a]-tetrabromobenzenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-a]-tetraphenylbenzenebutyric acid
 4-hydroxy-4-(p-cyclohexylphenyl)-[2,3-d]-imidazolebutyric acid

EXAMPLE 8

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4-keto-4-(4'-cyclohexyl-3'-nitrophenyl)butyric acid

To 100 ml. of fuming nitric acid, cooled to -10° C., is added portionwise 4 grams of 4-keto-4-(p-cyclohexylphenyl)butyric acid. This reaction mixture is stirred for 15 minutes and then poured onto ice. The mixture is then extracted with chloroform, washed with water, dried over sodium sulfate and concentrated in vacuo to yield 4-keto-4-(4'-cyclohexyl-3'-nitrophenyl)butyric acid as an oil. This is recrystallized from benzene-petroleum ether (M.P. 119–123° C.).

Following the procedure of Example 8 above, but substituting for 4-keto-4-(p-cyclohexylphenyl)butyric acid an equimolar amount of the products of Table II, Example 1; Table I, Example 5; Table I, Example 6; and Table I, Example 7, there is obtained the corresponding nitrated product.

EXAMPLE 9

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4-keto-4-(4'-cyclohexyl-3'-aminophenyl)butyric acid

To one gram of 4-keto-4-(4'-cyclohexyl-3'-nitrophenyl)butyric acid, 50 ml. of ethanol is added and 0.5 gram of platinum oxide, and this is reduced over hydrogen. The reaction mixture is then filtered and evaporated in vacuo to yield 4-keto-4-(4'-cyclohexyl-3'-aminophenyl)butyric acid as a solid. This is then recrystallized from ethanol (M.P. 165.5–169° C.).

Following the procedure of Example 9 above, but substituting for 4-keto-4-(4'-cyclohexyl-3'-nitrophenyl)butyric acid an equimolar amount of the nitrated products that are not unsaturated obtained in Example 8, there is obtained the corresponding 3'-amino phenylbutyric acid.

EXAMPLE 10

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Methyl 4-keto-4-(4'-cyclohexyl-3'-chlorophenyl)butyrate
 Methyl 4-keto-4-(4'-cyclohexyl-3'-hydroxyphenyl)butyrate

To 4.4 grams of methyl 4-keto-4-(4'-cyclohexyl-3'-aminophenyl)butyrate suspended in 125 ml. of 80% hydrochloric acid and cooled to 0° C., is added dropwise a solution of 1.17 grams of sodium nitrite in 15 ml. of water. After about 10 minutes, a solution of 8.42 grams of cuprous chloride in 200 ml. of 50% hydrochloric acid is added portionwise and stirred for 15 hours. The reaction mixture is then poured onto ice-water and extracted with chloroform. This is dried over sodium sulfate and concentrated in vacuo to a solid which is chromatographed on silica gel; elution ether-petroleum ether (15–25%) to give methyl 4-keto-4-(4'-cyclohexyl-3'-hydroxyphenyl)butyrate eluted first (M.P. 155–157° C.), followed by methyl 4-keto-4-(4'-cyclohexyl-3'-chlorophenyl)butyrate.

Following the procedure of Example 10 above, but substituting for methyl 4-keto-4-(4'-cyclohexyl-3'-aminophenyl)butyrate an equimolar amount of the 3'-aminophenyl butyric acid compounds obtained from Example 9, there is obtained the corresponding 3'-chlorophenyl butyric acid and 3'-hydroxyphenyl butyric acid.

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EXAMPLE 11

Methyl 4-keto-4-(4'-cyclohexyl-3'-methylamino-phenyl)butyrate

To a solution of 0.01 mole of methyl 4-keto-4-(4'-cyclohexyl-3'-aminophenyl)butyrate in 100 ml. of benzene is added 0.01 mole of methyl iodide. The reaction mixture is stirred overnight at room temperature, filtered and concentrated. The residue is chromatographed on silica gel and eluted with ether-petroleum ether (5-90%) to give methyl 4-keto-4-(4'-cyclohexyl-3'-methylamino-phenyl)butyrate.

Following the procedure of Example 11 above, but substituting for methyl 4-keto-4-(4'-cyclohexyl-3'-aminophenyl)butyrate an equimolar amount of the 3'-aminophenyl butyric acid ester compounds obtained from Example 9, there is obtained the corresponding 3'-methylaminophenyl butyric acid ester.

EXAMPLE 12

Methyl 4-keto-4-(4'-cyclohexyl-3'-dimethylaminophenyl)-butyrate

A solution of .0046 mole of methyl 4-keto-4-(4'-cyclohexyl-3'-nitrophenyl)butyrate and 1.6 ml. of 37% formaldehyde in 50 ml. of methanol is hydrogenated over 0.5 gram of 5% palladium-on-charcoal under 42 lbs. of hydrogen pressure until 5 equivalents of hydrogen are absorbed. The catalyst is filtered off and the filtrate is evaporated in vacuo. The oily residue is dissolved in absolute alcohol, treated with hydrogen chloride gas and then evaporated to dryness, whereupon it crystallizes. The methyl 4-keto-4-(4'-cyclohexyl-3'-dimethylaminophenyl)butyrate hydrochloride is recrystallized from ethanol.

Following the procedure of Example 12 above, but substituting for methyl 4-keto-4-(4'-cyclohexyl-3'-nitrophenyl)butyrate an equimolar amount of the nitrated products obtained in Example 8, there is obtained the corresponding 3'-dimethylaminophenylbutyric acid.

EXAMPLE 13

Methyl 4-keto-4-(4'-cyclohexyl-3'-methoxyphenyl)butyrate

To a well stirred suspension of 0.01 mole of sodium hydride in 25 ml. of dry dimethylformamide, which has been cooled to 0° C., is added dropwise a solution of 0.01 mole of methyl 4-keto-4-(4'-cyclohexyl-3'-hydroxyphenyl)butyrate in 10 ml. of dimethylformamide. The reaction mixture is stirred for 15 minutes and 0.015 mole of methyl iodide is then added dropwise. The mixture is allowed to stir overnight at room temperature, 200 ml. of water is added, and the resulting mixture is extracted well with ether. The combined ether extracts are washed well with water, dried over sodium sulfate, and concentrated. The residue is chromatographed on silica gel and eluted with ether-petroleum ether (10-80%) to yield methyl 4-keto-4-(4'-cyclohexyl-3'-methoxyphenyl)-butyrate.

Following the procedure of Example 13 above, but substituting for methyl 4-keto-4-(4'-cyclohexyl-3'-methoxyphenyl)butyrate an equimolar amount of the 3'-hydroxyphenyl butyric acid product obtained in Example 10, there is obtained the corresponding 3'-methoxyphenyl butyric acid ester product.

EXAMPLE 14

Methyl 4-keto-4-(p-cyclohexylphenyl)butyrate

To an ether solution (75 ml.) of 4-keto-4-(p-cyclohexylphenyl)butyric acid (.02 mole) there is added an ether solution (150 ml.) of diazomethane (ca. 0.02 mole). This is allowed to stand for two hours and then the ether is evaporated off slowly with mild warming to yield methyl 4-keto-4-(p-cyclohexylphenyl)butyrate.

In a similar manner, the acids of these examples are converted to the corresponding methyl esters.

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EXAMPLE 15

Benzyl 4-(p-cyclohexylphenyl)-3-ketobutyrate

(A) 4-(p-cyclohexylphenyl)-3-ketobutyryl chloride.—To a solution of 0.015 mole of 4-(p-cyclohexylphenyl)-3-ketobutyric acid in 25 ml. of anhydrous benzene is added 2.15 grams (.018 mole) of thionyl chloride. The reaction mixture is refluxed for 1½ hours and the solvent is evaporated in vacuo to yield 4-(p-cyclohexylphenyl)-3-ketobutyryl chloride.

(B) Benzyl 4-(p-cyclohexylphenyl)-3-ketobutyrate.—To 20 ml. of benzyl alcohol is added the 3-ketobutyryl chloride from Step A. The mixture is heated on a steam-bath for ¾ hour, and then evaporated to dryness in vacuo to yield benzyl 4-(p-cyclohexylphenyl)-3-ketobutyrate.

In a similar manner, the acids of these examples are converted to the corresponding esters.

EXAMPLE 16

4-keto-4-(p-cyclohexylphenyl)butyryl morpholide

(A) 4-keto-4-(p-cyclohexylphenyl)butyryl chloride.—To a solution of 0.022 mole of 4-keto-4-(p-cyclohexylphenyl)butyric acid in 30 ml. of anhydrous benzene is added 2.86 grams (0.024 mole) of thionyl chloride. The reaction mixture is refluxed for 1½ hours and the solvent evaporated in vacuo to yield 4-keto-4-(p-cyclohexylphenyl)butyryl chloride.

(B) 4-keto-4-(p-cyclohexylphenyl)butyryl morpholide.—To 20 ml. of morpholine is added dropwise, and with cooling, the butyryl chloride prepared above. The reaction mixture is stirred at room temperature for two hours, acidified with 2.5 N hydrochloric acid, and extracted well with methylene chloride. The combined methylene chloride extracts are then extracted with 2.5 N sodium hydroxide, washed with water, dried over sodium sulfate, and concentrated in vacuo to yield 4-keto-4-(p-cyclohexylphenyl)butyryl morpholide.

When ammonia, methylamine, diethylamine, cyclopropylamine, piperidine, piperazine, homopiperazine and pyrrolidine are used in place of morpholine in the procedure described above, then the amido, methylamido, diethylamido, cyclopropylamido, piperidino, piperazino, homopiperazino and pyrrolidino amido of 4-keto-4-(p-cyclohexylphenyl)butyric acid are prepared.

In a similar manner, the acids of these examples are converted to the corresponding amides.

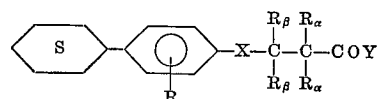
EXAMPLE 17

The following compounds are tested in rats to determine their ability to inhibit edema induced by injection of an inflammatory agent into the tissues of the foot of a rat and compared against non-inflamed controls by the procedure of C. A. Winter, Proceedings Society of Experimental Biology and Medicine, 1962, III, 544.

Compound	Edema dose, mg./kg.	Percent inhibition
4-keto-4-(p-cyclohexyl-3'-nitrophenyl)butyric acid	30	17
4-keto-4-(p-cyclohexyl-3'-aminophenyl)butyric acid	10	46
methyl 4-keto-4-(p-cyclohexyl-3'-chlorophenyl)-butyrate	9	51
4-keto-4-(p-cyclohexylphenyl)-2-butenic acid	10	7
4-keto-4-(p-cyclohexylphenyl)-butyric acid	10	14

We claim:

1. A compound of the formula:



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where

X is

R_a and R_β are hydrogen or lower alkyl

R is halo

Y is —OH, lower alkoxy, benzyloxy or OM where M is an alkali, alkaline earth or aluminum metal.

2. A compound according to claim 1 where R is 3'-chloro.

3. A compound according to claim 1 where R is 3'-chloro and Y is —OH.

4. A compound according to claim 1 wherein R_a and R_β are hydrogen or lower alkyl; and R is chloro.

5. 4-keto-4-(3'-chloro-4'-cyclohexyl)phenylbutyric acid.

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